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NREM and REM Sleep: Complementary Roles in Recovery after Wakefulness

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Abstract

The overall function of sleep is hypothesized to provide "recovery" after preceding waking activities, thereby ensuring optimal functioning during subsequent wakefulness. However, the functional significance of the temporal dynamics of sleep, manifested in the slow homeostatic process and the alternation between non–rapid eye movement (NREM) and REM sleep remains unclear. We propose that NREM and REM sleep have distinct and complementary contributions to the overall function of sleep. Specifically, we suggest that cortical slow oscillations, occurring within specific functionally interconnected neuronal networks during NREM sleep, enable information processing, synaptic plasticity, and prophylactic cellular maintenance ("recovery process"). In turn, periodic excursions into an activated brain state—REM sleep—appear to be ideally placed to perform "selection" of brain networks, which have benefited from the process of "recovery," based on their offline performance. Such two-stage modus operandi of the sleep process would ensure that its functions are fulfilled according to the current need and in the shortest time possible. Our hypothesis accounts for the overall architecture of normal sleep and opens up new perspectives for understanding pathological conditions associated with abnormal sleep patterns.

Keywords

sleep, wakefulness, NREM sleep, REM sleep, recovery

Introduction

Sleep is a phenomenon of astounding complexity, which makes it difficult to understand and even define unequivocally (Deboer 2013; Vyazovskiy and Harris 2013). It can be viewed as behavior, a brain state, and a process, which are intricately interrelated, and manifest themselves at many distinct spatiotemporal scales. Sleep is regulated by circadian time (Fisher and others 2013), preceding sleep-wake history (Achermann and others 1993), and while asleep, the brain switches periodically between two markedly different states—non–rapid eye movement (NREM) sleep and (REM) sleep (Saper and others 2010), which are distinguished by specific types of brain activity (Zamboni and others 1999; Buzsaki and others 2013). Specifically, a closer look at NREM sleep, also called slow-wave sleep, reveals that it is characterized by a regular occurrence of local and global slow cortical oscillations, visible at the level of the EEG as slow waves (Destexhe and others 1999; Massimini and others 2004; Vyazovskiy and Harris 2013). Throughout NREM sleep, especially during its lighter stages and toward a transition into REM sleep, another type of activity is apparent, so-called sleep spindles. These involve the thalamus and through dynamic corticothalamic interactions emerge quasi-independently at specific brain locations and never across the whole brain at once (Andrillon and others 2011; Bonjean and others 2011; De Gennaro and Ferrara 2003; Vyazovskiy and others 2004b). In contrast, during REM sleep, the brain is about as active as it is in waking, although some notable differences with respect to the regional patterns of activation have been found in humans (Maquet and others 2005). The EEG in both humans and animals is dominated by theta- and faster rhythms (Cantero and others 2003; Huber and others 2000; Nishida and others 2009; Vyazovskiy and others 2004a), which arise from bidirectional interactions of cortical, hippocampal, and subcortical networks (Brown and others 2012; Buzsáki 2006). Are all these sleep-related phenomena (Fig. 1) related to each other and what is the functional meaning of the overall complexity of the sleep process?

In this review article, we advance a hypothesis that attempts to reconcile numerous phenomena associated

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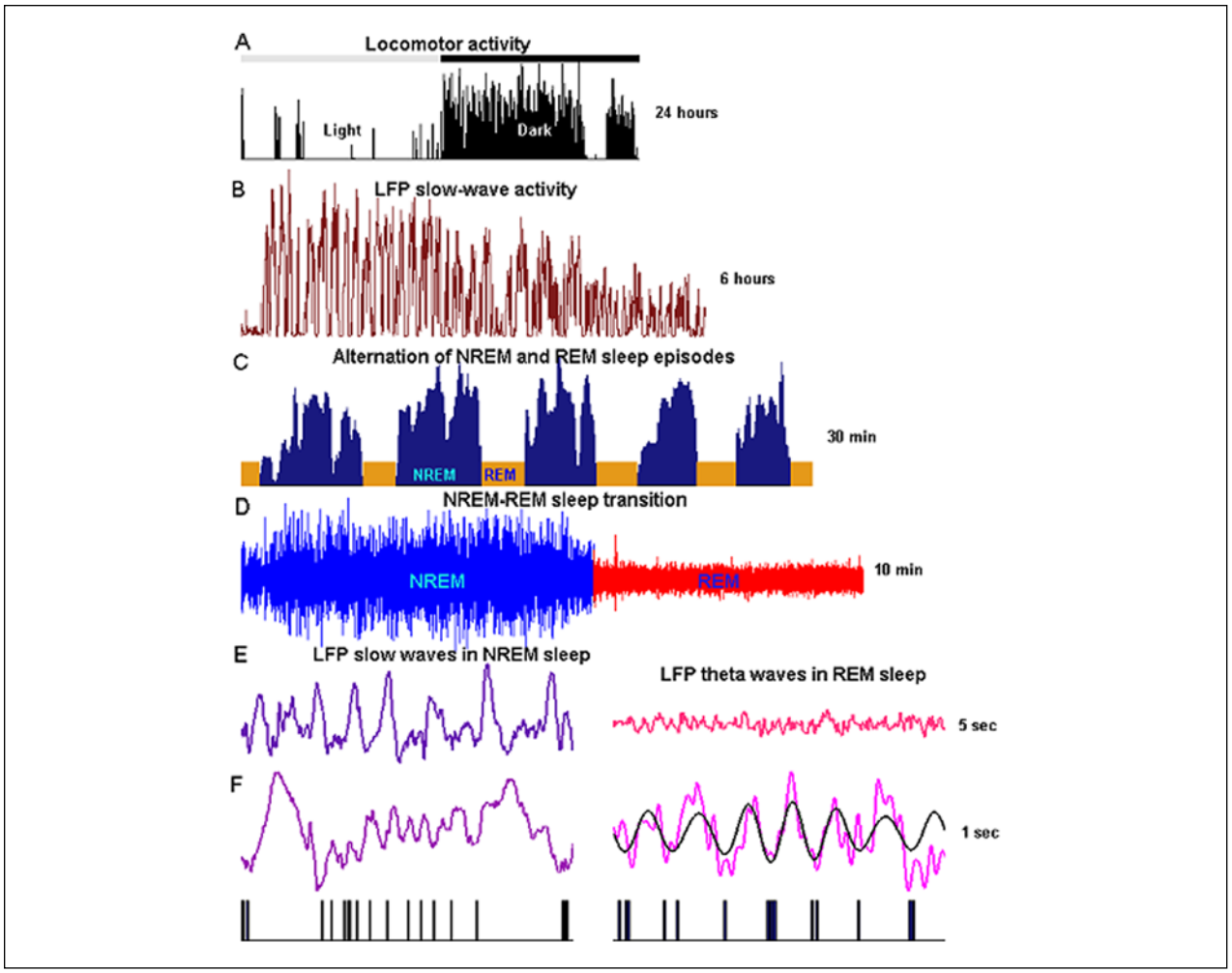

Figure 1. The temporal complexity of sleep. (A) The daily profile of locomotor activity in one individual mouse during 24 hours (LD 12:12, bars on the top). Note that most activity occurs during the dark period, whereas during the light period the animal is predominantly immobile, and likely asleep. (B) The typical homeostatic profile of cortical local field potential (LFP) slow wave activity (SWA, 0.5–4 Hz) in non–rapid eye movement (NREM) sleep during a 6-hour period of the light period. Note that SWA is initially high and declines progressively across the period of sleep. (C) Cortical SWA during five consecutive NREM sleep episodes, each lasting ~5 minutes. Note that NREM sleep is interrupted regularly by shorter episodes of REM sleep. (D) The LFP recorded from the frontal cortex in a rat during a typical episode of NREM sleep (blue) followed by REM sleep episode (red). NREM sleep is characterized by high-amplitude LFP slow (0.5–4 Hz) waves, which are replaced by regular theta (6–9 Hz) activity of a lower amplitude during subsequent REM sleep. (E) Representative traces of the LFP shown at higher resolution in NREM sleep (blue), dominated by high-amplitude slow waves, and REM sleep (red), rich of theta-activity and faster rhythms. (F) A closer look at the LFP signals in NREM sleep (left), where two slow waves are visible and a spindle (~7–15 Hz) in between, and in REM sleep, where regular theta-oscillation (black) is apparent. Bars below depict an expected corresponding pattern of cortical neuronal activity (each vertical line is a spike).

with sleep at many spatial and temporal levels with the proposed "recovery" function of sleep. Our hypothesis is grounded on the observation that sleep is homeostatically regulated (Borbely 1982). The main postulate of sleep homeostasis is "the longer we are active, the deeper is our sleep" (Daan and others 1984). In other words, it implies that the need for sleep ("sleep pressure") increases in proportion to the preceding duration of waking, and then dissipates during the ensuing sleep in proportion to its duration and intensity. The homeostatic regulation of sleep is manifested in systematic changes of the main defining characteristic of NREM sleep–EEG slow-wave activity (SWA, 0.5–4.0 Hz), which is high at the beginning of a sleep period and gradually decreases during the course of sleep, whereas prolonged waking is invariably followed by a proportional increase in sleep SWA (Cirelli and Tononi 2008; Franken and others 2001; Tobler 2005; Vyazovskiy and Harris 2013; Vyazovskiy and others 2006; Vyazovskiy and Tobler 2005). It was proposed that NREM sleep occurs in a local, use-dependent manner and

is ultimately a property of cortical networks (Krueger and Obal 1993; Krueger and others 2008). There is substantial evidence showing that sleep is implicated in a variety of restorative processes at molecular, cellular and network levels and in synaptic plasticity (Abel and others 2013; Cirelli and Tononi 2008; Scharf and others 2008; Vyazovskiy and Harris 2013), which we altogether refer to as "recovery." It is likely that the recovery functions of NREM sleep are related to the occurrence of the thalamocortical slow oscillation (Buzsáki 2006; Crunelli and Hughes 2009; Steriade and others 2001). The purpose of a down-state of the slow oscillation could be to provide restoration with respect to energy homeostasis, cellular maintenance/repair, or biosynthetic processes (Mackiewicz and others 2007; Maret and others 2007; Scharf and others 2008; Vyazovskiy and Harris 2013; Wisor 2012). At the same time, the role of an up-state was proposed to provide an opportunity for selective interactions between functionally interconnected neurons within cortical and subcortical networks, thereby facilitating information transfer and serving plastic processes or memory consolidation (Battaglia and others 2004; Destexhe and others 2007; Diekelmann and Born 2010; Tononi and Cirelli 2006). There are two fundamental questions that need to be addressed, and which will be the focus of this article. First, how is it ensured that the brain receives the appropriate amount of recovery according to its needs? Second, what is the role of periodic excursions into an activated sleep state—REM sleep?

REM Sleep: Its Regulation and Proposed Functions

At quasi-regular intervals, NREM sleep episodes terminate and the brain transitions into another sleep state, which is called REM sleep or paradoxical sleep (Dement 1958; Jones 2004; Jouvet 1965; McCarley and Hobson 1975). The defining features of REM sleep are skeletal muscle atonia, rapid eye movements, the presence of EEG theta (~6–9 Hz) waves originating from the hippocampus, and the ponto-geniculo-occipital (PGO) waves (Callaway and others 1987; Datta 2010; Karashima and others 2010; Siegel 2011). In physiological conditions, REM sleep episodes are generally shorter than episodes of NREM sleep, and the NREM-REM sleep cycle repeats itself several times before the animal wakes up (Achermann and others 1993; Benington and Heller 1994; Trachsel and others 1991; Franken 2002; Zamboni and others 1999; Vyazovskiy and Tobler 2012).

REM sleep has always been a "difficult" case with respect to its regulation and function (Siegel 2011). Early theories pertaining to the regulation of REM sleep suggested that the regular occurrence of REM sleep episodes is an expression of a so-called basic rest-activity cycle (Kleitman 1982). Alternatively, state-dependent theories of REM sleep regulation suggested that the need (or pressure) for REM sleep increases during waking, NREM sleep, or both (Benington and Heller 1994). Specifically, because the duration of a REM sleep episode correlates significantly with the duration of the following NREM sleep episode, it was proposed that REM sleep "compensates for some process that takes place during NREM sleep" (Barbato and Wehr 1998; Benington and Heller 1994). However, selective or total sleep deprivation experiments suggested that preceding long-term and short-term history of waking and sleep also plays a role (Endo and others 1997; Franken 2002; Ocampo-Garces and Vivaldi 2002). Interestingly, REM sleep expression is not only determined by preceding history but is also subject to circadian rhythmicity (Dijk and Czeisler 1995; Kantor and others 2009). Moreover, in both humans and animals the amount as well as spontaneous EEG activity in REM sleep were shown to be under genetic control (Buckelmuller and others 2006; Franken and others 1998; Millstein and others 2011).

The biological function of REM sleep still remains a mystery (Siegel 2011), although several theories have been advanced (Hobson 2009; Horne 2000; Horne 2013; Roffwarg and others 1966; Siegel 2005). According to one theory, when the brain is isolated from external inputs during REM sleep, random patterns of activation can be generated that are useful for elimination of "parasitic modes" of activity (Crick and Mitchison 1983). It was also suggested that REM sleep is necessary for brain development (Roffwarg and others 1966) or may serve the function of periodically activating the brain during sleep without awakening the subject and disturbing the continuity of sleep (Horne 2013; Vertes and Eastman 2000). In addition, there is evidence that REM sleep plays a role in memory formation (Karni and others 1994; Perogamvros and others 2013; Rasch and Born 2013; Smith 1985; Stickgold 1998; Watts and others 2012), neuronal plasticity and excitability (Grosmark and others 2012; Poe and others 2010; Ribeiro and Nicolelis 2004), and in processing of emotional information (Baran and others 2012; Gujar and others 2011).

Subcortical regions involved in the regulation of NREM and REM sleep have been elucidated to a large extent (Fort and others 2009; Saper and others 2010; Szymusiak and McGinty 2008). According to the reciprocal interaction model, a brainstem circuitry of mutually inhibiting cholinergic and monoaminergic nuclei can account for the NREM-REM cycle (Hobson and others 1975). More recently, a role for mutually inhibiting GABAergic neurons contained within REM-on and REM-off brainstem regions has been postulated (Boissard and others 2002; Lu and others 2006; Sapin and others 2009; Sastre and others 1996; Vanini and others 2007; Xi

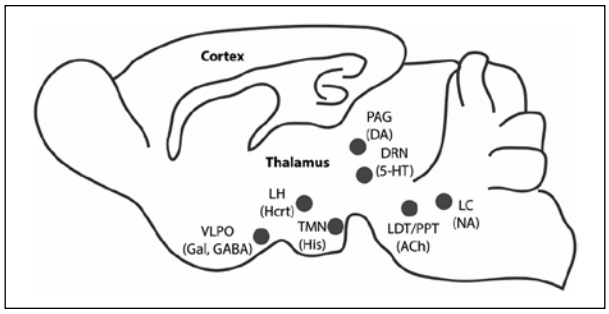

Figure 2. The anatomical location of major subcortical regions involved in regulation of waking and sleep. The main subcortical nuclei and areas, which have been shown to be crucial for regulation of cortical arousal and sleep, are shown on a saggital section of a rodent brain, and their main neurotransmitters or neuromodulators. DRN = dorsal Raphe nucleus, serotoninergic (5-HT); LC = locus coeruleus, noradrenergic (NA); LDT = laterodorsal tegmentum; and PPT = pedunculopontine tegmentum, cholinergic (ACh); LH = lateral hypothalamus including hypocretin/orexin expressing neurons (Hcrt); PAG = periaqueductal gray, including dopaminergic neurons (DA); POA = preoptic area; and VLPO = ventrolateral preoptic area, GABAergic and containing galanin (Gal) expressing neurons; TMN = tuberomammillary nucleus, histaminergic (His).

and others 1999). These REM sleep-regulatory regions appear to be under the control of the hypothalamus (Mignot and others 2002; Saper and others 2005). Specifically, the onset of REM sleep may be regulated by hypothalamic GABA neurons through the recruitment of the extended ventrolateral preoptic area (eVLPO) (Lu and others 2002). In addition, a subset of melanin-concentrating hormone (MCH) neurons in the lateral hypothalamus are active at REM onset and fire exclusively during REM sleep (Hassani and others 2009), whereas MCH-negative GABA neurons in the lateral hypothalamus increase firing as NREM progresses to REM sleep (Hassani and others 2010). Exit from REM sleep seems to be regulated by waking-promoting systems such as the pontine and medullary monoaminergic neurons, tuberomammilary histaminergic neurons, and the hypothalamic orexin/hypocretin neurons (Fort and others 2009).

Although great efforts have been devoted to delineating the brain systems that are necessary and sufficient for the regular transitions from NREM sleep to REM sleep (Fig. 2), fundamental questions remain: Why should REM sleep exist in the first place, and why it is occurring regularly throughout the sleep period?

"Recovery" and "Selection" during Sleep

We argue that the roles of REM and NREM sleep as well as their interactions can only be understood by considering the microstructure of brain activity on a fine temporal and spatial scale, in relation to the global temporal evolution of sleep stages and the slow homeostatic process (Fig. 1). If we look closely at the cortical activity during NREM sleep, it is apparent that it occurs in discrete steps. This is reflected in a sequential occurrence of EEG slow waves, which arise from oscillations between active (up, ON) and inactive (down, OFF) states of individual neurons (Buzsaki and others 2012; Steriade and others 2001; Vyazovskiy and others 2009). Crucially, individual slow waves appear to be idiosyncratic and dynamic entities, as they do not occur everywhere at the same time, but are often local, have a unique site of origin, involve specific cortical areas, have a variable "shape," and follow a unique route of propagation (Massimini and others 2004; Nir and others 2011; Riedner and others 2007; Riedner and others 2011; Sirota and Buzsaki 2005; Timofeev 2013; Vyazovskiy and others 2007a; Vyazovskiy and others 2007b; Vyazovskiy and others 2011). What is the functional meaning behind the rich diversity among individual slow waves and what determines the temporal and spatial pattern of their occurrence?

We propose that during NREM sleep individual cortical functional networks are sequentially recruited into the slow waves, into which any NREM sleep episode is partitioned (Fig. 3). Specifically, during an individual slow wave, a neuronal network is recruited simultaneously in an ON-period, where all neurons of the network engage in synaptic and/or spiking activity, which is followed by a synchronized silence (OFF-period) *within* the same network. We posit that during physiological sleep, this process continues until all the networks have expressed a certain minimal number of slow oscillations, as required to obtain the necessary "recovery" after their respective preceding activities. As mentioned above, we use the term "recovery" in a broad sense, including a variety of processes at molecular, cellular, and network levels, such as synaptic plasticity, regulation of neuronal excitability, replenishment of energy stores, cellular and subcellular membrane repair, and other kinds of prophylactic cellular maintenance (Vyazovskiy and Harris 2013). Given the anatomical complexity of the brain, the large number of highly specialized distributed networks of various configurations and their different history of activity during preceding waking, it appears to be a formidable task to provide recovery to specific networks precisely according to their need. First, newly formed neuronal networks that have just emerged as a result of specific novel waking experience are likely to need a very different amount and kind of recovery, compared with those networks that were "used" heavily, or remained "dormant" during the preceding waking period. Second, some networks may consist of highly heterogeneous large populations of polysynaptically interconnected neurons located across several distant cortical areas, whereas others may be small, mostly locally interconnected, and consist of a

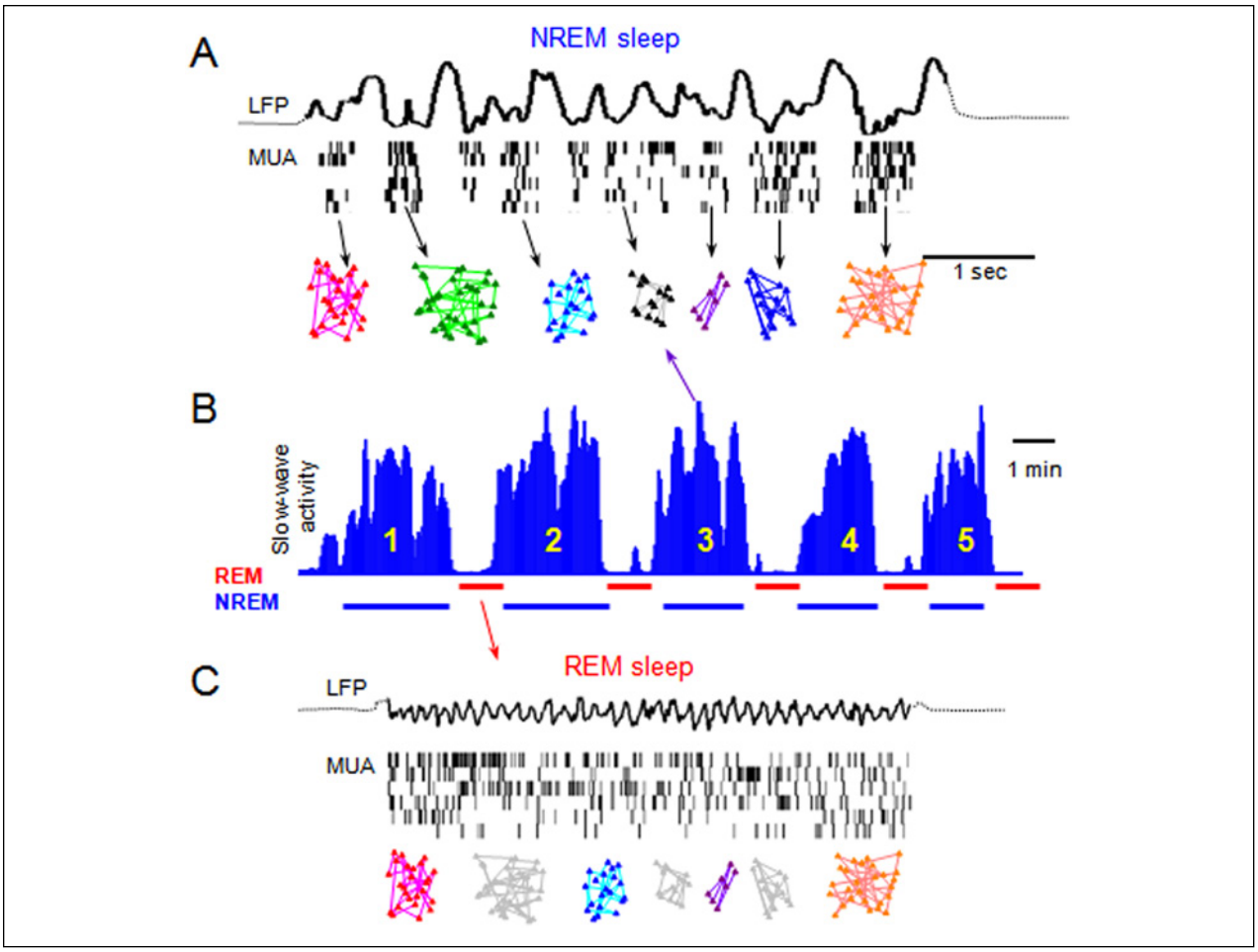

Figure 3. Outline of the hypothesis: cortical mechanisms. We hypothesize that the cortical activity during NREM sleep (A) occurs in discrete steps, manifested in the occurrence of local field potential (LFP) slow waves arising from a synchronous involvement of specific functionally interconnected neuronal networks in an active state (high multiunit activity, MUA), followed by silent periods, when spiking and synaptic activity within the corresponding networks is suspended. Each LFP slow wave has a unique site of origin and spatial configuration determined by the size and composition of the neuronal network involved (arrows). Individual neurons are schematically shown as triangles, and connections within a network by lines. Note that different colors for the networks are used to emphasize that a unique network is recruited during each slow wave. We hypothesize that slow waves occur one after another throughout a NREM sleep episode (B, five consecutive episodes are shown) until all functionally interconnected networks have expressed a certain minimal number of slow oscillations, as dictated by their need for recovery, whereby the NREM sleep episode is terminated and followed by a REM sleep episode. (C) During the regular excursions into REM sleep, a selection process takes place, which consists in identifying those networks that have already obtained the necessary recovery during previous NREM sleep (shown below in gray color), to exclude them from the process of recovery in subsequent NREM sleep episodes.

homogenous functionally specialized population. Finally, the same neurons may participate in more than one functional network (and likely do so), and therefore the expression of the slow oscillation across many networks at the same time needs to be precisely coordinated.

The first question that needs to be addressed is what are the mechanisms responsible for synchronizing the periods of activity and silence between neurons within a given functional network? Within-network synchrony is important for two reasons. First, as has been recently suggested, synchronous occurrence of sustained uninterrupted down states within functionally interconnected cortical networks enables more efficient prophylactic cellular maintenance (Vyazovskiy and Harris 2013). Second, synchronized coordinated increase of network activity during an up-state or an ON-period (Luczak and others 2007) may provide an opportunity for communication between functionally connected neurons, enabling information processing and synaptic plasticity (Sirota and Buzsaki 2005). This is likely necessary as synchronous

activation of a specific network allows the neurons, distributed across the brain and embedded in many different networks, to temporarily (functionally) uncouple from the rest of the brain. The specific mechanism by which the networks self-organize in time and space, and how it is related to their need for recovery, remains to be determined, although some possibilities can be suggested. For example, a population of sleep-active NOS-expressing cortical interneurons, which has been identified recently, appears to be ideally placed to link preceding sleep-wake history with a compensatory increase of cortical slow-wave activity (Kilduff and others 2011; Morairty and others 2013). On the other hand, neuroligin, which is a cell adhesion postsynaptic protein, critically involved in the formation and stabilization of neural networks, was shown to link preceding neuronal activity with homeostatic sleep regulation (El Helou and others 2013), and may also play a role.

Our model predicts that during the course of the night (or day in rodents), as sleep progresses toward the final awakening, fewer (and more localized) networks need to be recruited in a synchronous slow oscillation, because many of them have already obtained the necessary recovery (Fig. 4). It is likely that large, distributed, and/or more strongly interconnected networks gain priority in this process, whereas recovery within smaller networks scattered across the brain would predominantly occur toward the end of the sleep period. An increased occurrence of local patterns of activity in the second half of sleep (Nir and others 2011; Terzaghi and others 2012; Vyazovskiy and others 2011) and a decrease in EEG synchronization during sleep across time (Vyazovskiy and others 2004a) may account for the progressive decrease of EEG slow-wave activity during sleep documented in several species (Tobler 2005). Thus, we propose that NREM sleep episodes occur throughout the entire sleep period, until all the networks in the brain have expressed the necessary number of slow oscillations to obtain recovery corresponding to their need. The next question is what determines whether a specific network has obtained the necessary recovery to enable its optimal performance during waking?

A strong selective pressure must have led to an emergence of an efficient mechanism that ensures that recovery at the level of individual networks is completed in the shortest time possible to avoid the dangers associated with sleep. We propose that in order to ensure that the recovery functions provided by NREM sleep are fulfilled in a controlled, systematic, and efficient manner, an additional regulatory process must be implemented to enable the selection of those circuits that have already obtained the necessary recovery and are ready for optimal functioning during waking. In theory, one solution could be to simply wake up at regular intervals and attempt to initiate typical waking behaviors. However, this strategy is highly energy demanding and time consuming, as it takes considerable time to dissipate sleep inertia, which is associated with suboptimal performance (Krueger and Tononi 2011; Tassi and others 2006). Moreover, if this strategy were chosen, it would require that the performance is tested each time across a broad repertoire of typical species-specific waking behaviors, and often during a suboptimal time of the 24-hour day. Therefore, a more economical and safe solution would be to perform the selection process of brain networks while remaining "offline." It appears that regular excursions into REM

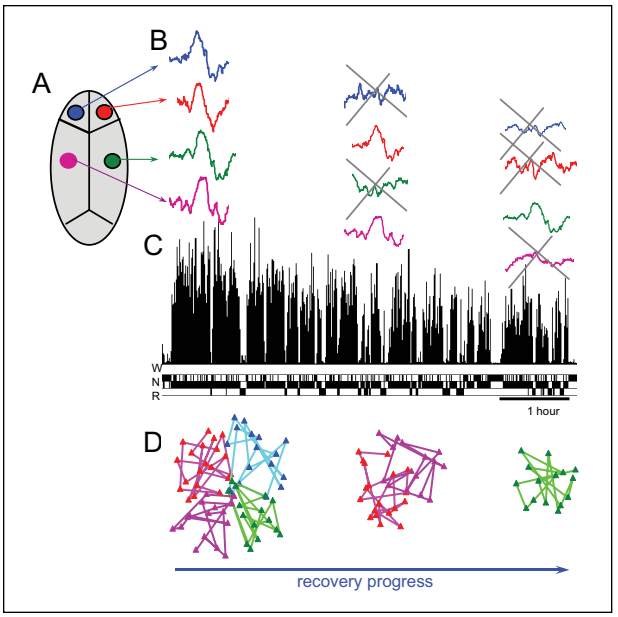

Figure 4. Spatial dynamics of LFP slow waves during NREM sleep. (A) Schematic diagram of the location of cortical local field potential (LFP) electrodes on the rat's skull (bilateral frontal: blue and red, and bilateral parietal: purple and green). (B) The hypothetic occurrence of slow waves recorded simultaneously in the four cortical locations (shown on panel A in corresponding colors) at the beginning, in the middle, and at the end of a typical period of undisturbed sleep. (C) A representative time course of LFP slow-wave activity (SWA, 0.5–4 Hz) in NREM sleep across sleep period. Note that SWA is initially high and shows a progressive decline across the sleep period. The corresponding hypnogram (waking: W, NREM sleep: N, and REM sleep: R) is shown below. We hypothesize that slow waves occur near-synchronously across distant cortical areas in early sleep but become more localized as sleep progresses, as most networks have obtained the necessary recovery. Subsequently, only a subset of cortical areas shows a slow wave simultaneously. This is overall reflected in a progressive decline of SWA across the sleep period. Bottom: Schematic depiction of the neuronal networks, which are simultaneously recruited in a slow oscillation in early and late sleep (colors correspond to cortical locations shown on panel A and slow waves show on panel B).

sleep are ideally suited to enable this function, by emulating the wake-like condition while remaining functionally disconnected from the physical environment. A conceptually similar "sensing" mechanism has been conjectured recently to account for periodic brain state shifts during prolonged physiological wakefulness (Vyazovskiy and Tobler 2012). Specifically, it was suggested that regular brief cessations of active behaviors, i.e. episodes of quiet wakefulness, may be viewed as attempts to initiate NREM sleep. We then proposed that a reduction in the activity of arousal-promoting nuclei during such periods of immobility could lead to a disinhibition of sleep promoting areas, which, if sleep pressure has attained a certain level, would facilitate an occurrence of global sleep. Likewise, we propose here that the overall temporal dynamics of NREM and REM sleep alternation—from sleep onset until final awakening—is ultimately determined by the balance between the processes of "recovery" and "selection."

Neuroanatomical Substrate of REM "Selection" Mechanism: The Two Systems

Based on this hypothesis, we predict the existence of two systems in the brain, which provide the neurophysiological substrate for the hypothetical selection mechanism provided during REM sleep. The "core" part enables offline representation of various waking behaviors. This could be achieved by a recruitment of specific cortico-subcortical circuits, to internally generate various pseudo-random behavioral patterns based on the past experiences of the individual. This notion is largely consistent with the tenets of the neural emulation theory, according to which inner models of the body and the environment can be run offline to produce "imagery, estimate outcomes of different actions, and evaluate and develop motor plans" (Churchland 2002; Grush 2004). Several cortical and subcortical areas such as the posterior parietal cortex, basal ganglia, and the cerebellum, have been proposed to participate in neural emulators, involved in the sensorimotor coordination (Churchland 2002). Consistent with our hypothesis, multiple cortical and subcortical areas, including higher order sensory and motor regions as well as limbic areas, are about as active during REM sleep as during waking, albeit with some differences (Dang-Vu and others 2010). Moreover, dynamic interactions between sensorimotor and higher-order associative areas, including the default-mode network, characterize REM sleep (Chow and others 2013). Obviously, the actual behaviors must be prevented during the process of selection, and so muscle atonia occurs during REM sleep to prevent them. Indeed, if muscle atonia during REM sleep is prevented by brainstem lesions, animals exhibit a variety of movements, such as head raising or locomotion (Henley and Morrison 1974; Mouret and others 1967). The suppression of muscle tone during the selection process may be also essential to prevent the sensory input from muscle proprioceptors, which could interfere with the internal dynamics while the neural emulator is at work. The suppression of noradrenergic activity, typical for REM sleep, may be a necessary prerequisite for disabling the voluntary muscle control (Burgess and Peever 2013). It is tempting to speculate that in order to generate purely offline states during the REM selection process, other senses, such as temperature sensitivity or pain perception, must also be depressed. This is consistent with the typical reduced thermoregulation in REM sleep (Parmeggiani 2003), and with reduced pain sensitivity on abrupt awakening from REM sleep, as compared to awakenings from stage 2 slow wave sleep (Daya and Bentley 2010).

The second part of the proposed mechanism, which we tentatively call an "integrator," is predicted based on the necessity to determine if most or all brain networks have already obtained the necessary recovery and to "decide" whether the animal is ready to wake up or needs to enter another NREM sleep episode. We speculate that the hypothetical circuit responsible for this function must comprise of a network that is capable of integrating cortical inputs, modulating the major subcortical sleep regulatory nuclei, and dynamically regulating global cortical states (Fig. 5). Although the exact mechanism by which the "integrator" enables communications between relevant cortical and subcortical areas remains to be identified, we suggest that the thalamus is well positioned to be involved.

It has been shown in both animals and humans that the transition from NREM to REM sleep is marked by the occurrence of sleep spindles. Spindles are periodically recurring bursts of thalamocortical activity occurring at a characteristic frequency of about 7 to 15 Hz within a burst (Luthi 2013). Notably, spindles occur throughout the episode of NREM sleep, often in a local manner (Nir and others 2011), but they are especially apparent at the NREM-REM transition (Vyazovskiy and others 2004b). Nucleus reticularis of the thalamus (TRN) has been implicated in the generation of sleep spindles (Astori and others 2011; Contreras and others 1993; Crunelli and Hughes 2009; Steriade 2006), and it has been shown that thalamic spindles survive decortication (Contreras and others 1996). Although the occurrence of spindles has been associated with synaptic plasticity and memory consolidation, their precise role remains unclear (Luthi 2013; Sejnowski and Destexhe 2000). It has been recently proposed that local occurrence of spindles during NREM sleep constrains and facilitates specific intracerebral communications (Nir and others 2011). We suggest that

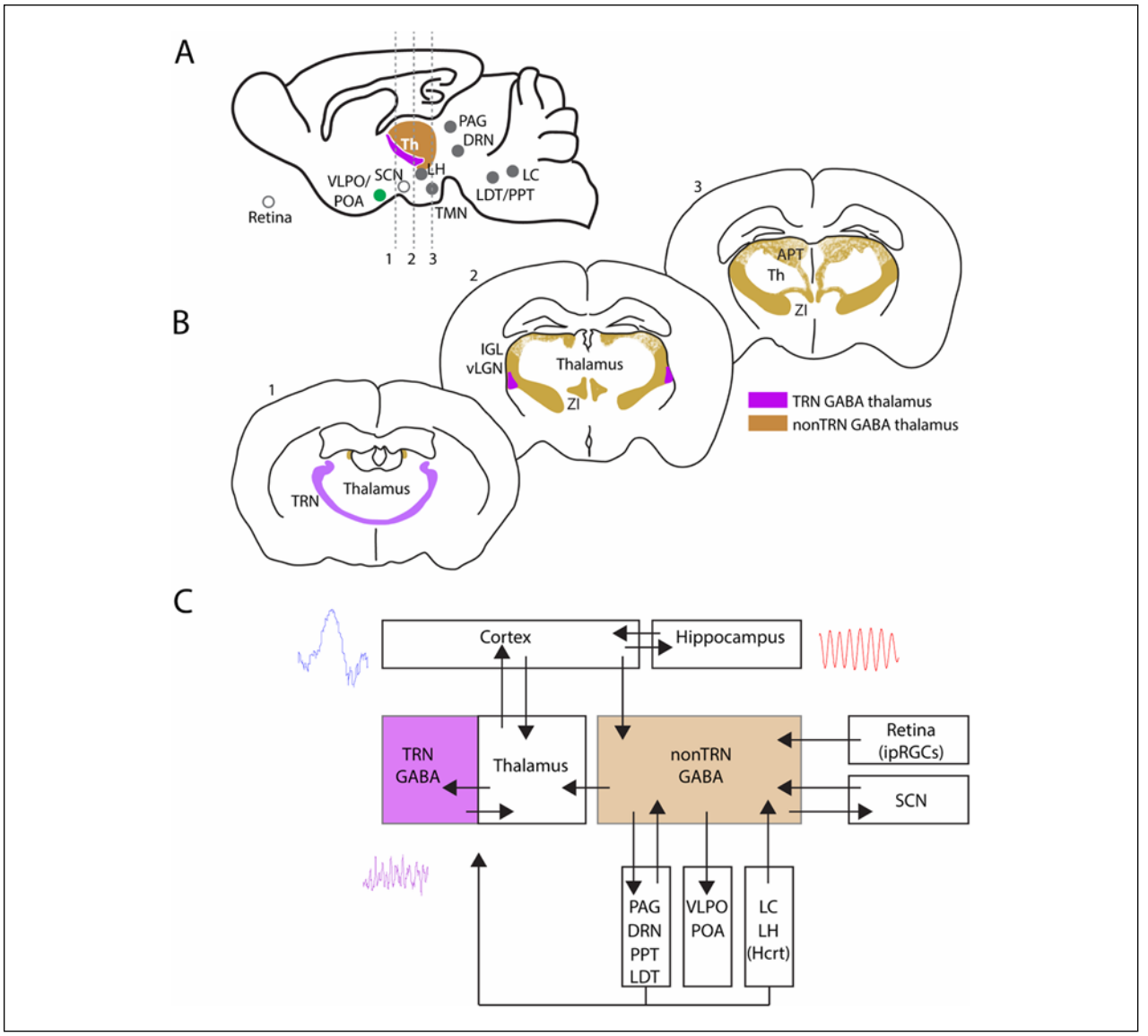

Figure 5. Complementary cohorts of inhibitory GABA neurons in the thalamus. In (A) the location of known subcortical regulators of sleep and wake and the position of reticular (TRN) and non-reticular (nonTRN) inhibitory thalamic neurons (purple and brown, respectively) in the mouse brain is schematically drawn. The location of sleep-on GABAergic neurons is indicated by a filled green circle; nuclei responsible for cortical activation are represented by filled gray circles. The location of neurons encoding circadian cues is represented as open gray circles. In (B): inhibitory neurons in the TRN are interneurons with projections restricted to the thalamic compartment. Inhibitory neurons that do not form the TRN are heterogeneous: they consist of local interneurons and projecting inhibitory neurons with targets within and outside the thalamus and complex afferents and neuromodulator expression; their anatomical position may condense to form nuclei or be interspersed with other neuron types. Within the thalamus, they can act on the intralaminar and midline thalamic relay nuclei thereby affecting global cortical states. In (C): the main differences in afferents and efferents of the two cohorts of thalamic inhibitory neurons in schematically presented. The GABA neurons in the nonTRN differ from their TRN counterparts in their reciprocal projections to cholinergic nuclei in the tegmentum (LDT and PPT), monoaminergic areas (including DRN and PAG) and the suprachiasmatic nucleus (SCN), incoming afferents from cortical areas, noradrenergic neurons in the LC, hypocretin/orexin neurons in the lateral hypothalamus and melanopsin-expressing ipRGCs in the retina and projections to hypothalamic areas including the preoptic area (POA, VLPO). Insets show predominant LFP wave-forms generated in the cortex (slow wave), the hippocampus (theta-waves), and the TRN (spindles). APT = anterior pretectum; DRN = dorsal Raphe nucleus; Hcrt = hypocretin/orexin neurons; IGL = intergeniculate leaflet; ipRGCs = intrinsically photosensitive retinal ganglion cells; LC = locus coeruleus; LDT = laterodorsal tegmentum; LH = lateral hypothalamus; PAG = periaqueductal gray; POA = preoptic area; PPT = pedunculopontine tegmentum; SCN = suprachiasmiatic nucleus; TMN = tubermamillary nucleus; TRN = thalamic reticular nucleus; vLGN = ventrolateral geniculate nucleus; VLPO = ventrolateral preoptic area; ZI = zona incerta.

localized occurrence of sleep spindles throughout NREM sleep episodes may reflect "tagging" of those networks that have presumably obtained the necessary recovery, for their inclusion in the selection process during subsequent REM sleep. We propose that after a certain critical number of tagged networks have been accumulated, the selection process is triggered, as reflected in an overall increased spindling at the NREM-REM sleep transition.

At this point, another anatomically distinct thalamic subsystem likely takes over the dominant role in coordinating the selection process. Specifically, we suggest that this consists of a complementary cohort of inhibitory thalamic GABA neurons (nonTRN-GABA neurons) (Bartho and others 2002; Bokor and others 2005; Delogu and others 2012). The nonTRN-GABA neurons of the thalamus are a heterogeneous group, characterized by a broad range of connections within and outside the thalamus, making it an attractive candidate for the role of conveying a cortically generated signal from the "core" of the selection mechanism to brainstem and hypothalamic regulators of NREM and REM sleep. It has been shown that some nonTRN-GABA neurons receive descending projections from prefrontal, infralimbic, and visual cortical areas (Vidal and others 2005; Vrang and others 2003) and form reciprocal connections with REM-on cholinergic and REM-off monoaminergic nuclei in the brainstem (Morin 2013; Morin and Blanchard 2005; Terenzi and others 1995). A conspicuous fraction of nonTRN-GABA neurons are located in the lateral geniculate nuclei, from where they send descending axons to the anterior hypothalamus and innervate sleep-on GABA nuclei in the median preoptic area and the eVLPO (Morin and Blanchard 1999). NonTRN-GABA neurons of the MCH subtype in the zona incerta (ZI) also provide an important GABA inhibition to the REM-off nuclei (Clement and others 2012). A recent study utilized an optogenetic approach, in which REM sleep episodes were prolonged by stimulation of hypothalamic MCH neurons (Jego and others 2013). Other nonTRN-GABA neurons control state-dependent gating of the higher order intralaminar and midline thalamic nuclei (Albrecht and others 1996; Antal and others 2010; Blitz and Regehr 2005; Bokor and others 2005; Munsch and others 2005; Zhao and others 2002), and thus modulate cortical state (Fig. 5).

In contrast to TRN-GABA neurons, nonTRN-GABA neurons display extensive connectivity with the circadian system. Specifically, nonTRN-GABA neurons that populate the non-image forming visual system (Delogu and others 2012), receive light information from conventional and intrinsically photosensitive retinal ganglion cells (ipRGCs) (Hankins and others 2008; Hattar and others 2002; Hattar and others 2006). IpRGCs detect light via an endogenous photoreceptor melanopsin (*Opn4*) and are required for photoentrainment of the circadian clock, the suppression of motor activity in nocturnal animals, and other physiological responses to light (Davies and others 2010; Hatori and others 2008; Peirson and Foster 2006). Importantly, ipRGCs have been implicated in the regulation of sleep (Altimus and others 2008; Lupi and others 2008; Tsai and others 2009), mood, and cognition (LeGates and others 2012). Acute light stimulation in nocturnal animals results in a rapid suppression of motor activity and concomitant induction of NREM sleep, which is then followed by REM sleep (Studholme and others 2013). A dense plexus of ipRGC-axon terminals innervates those nonTRN-GABA neurons that project to the master circadian clock at the hypothalamic suprachiasmatic nucleus (SCN) and the SCN sends reciprocal projections back to the same area (Morin 2013). Thus, there is substantial neuroanatomical evidence supporting the hypothesis of an integrative function of nonTRN-GABA neurons in the control of sleep.

Notably, most REM sleep episodes are terminated with a so-called brief awakening, associated with a surge of firing activity in the locus coeruleus (Gervasoni and others 1998). We suggest that an attempt to wake up after virtually every REM sleep episode is a manifestation of the neurophysiological mechanisms signaling the extent of the recovery process completed (Fig. 6). However, we suspect that it is not essential whether the actual awakening occurs from NREM or REM sleep, as long as all networks in the brain have benefited from the recovery processes in NREM sleep, and underwent selection during REM sleep. Indeed, brief awakenings occur regularly throughout a NREM sleep episode and, notably, their incidence correlates negatively with cortical EEG slow-wave activity in rats (Franken and others 1991; Trachsel and others 1991). Moreover, enhanced sleep pressure diminished the probability of awakening following the photostimulation of hypocretin neurons expressing light-activated cation channel ChR2 in mice (Carter and others 2009). Thus, the overall role of the integrator system that we postulate is to provide continuous bidirectional communications between the cortex and subcortical wake- and sleep-regulating areas throughout both NREM and REM sleep, to ensure that the animal wakes up when the process of recovery is "deemed" completed.

"Selection" Role of REM Sleep and Previous REM Sleep Hypotheses

Although our hypothesis requires direct empirical testing, we believe that it not only provides a useful conceptual framework for future experiments, but also appears to be compatible with many earlier findings and hypotheses. For example, one of the well-established phenomena is the "competing" relationship between NREM and REM sleep expression across the night (Beersma and others

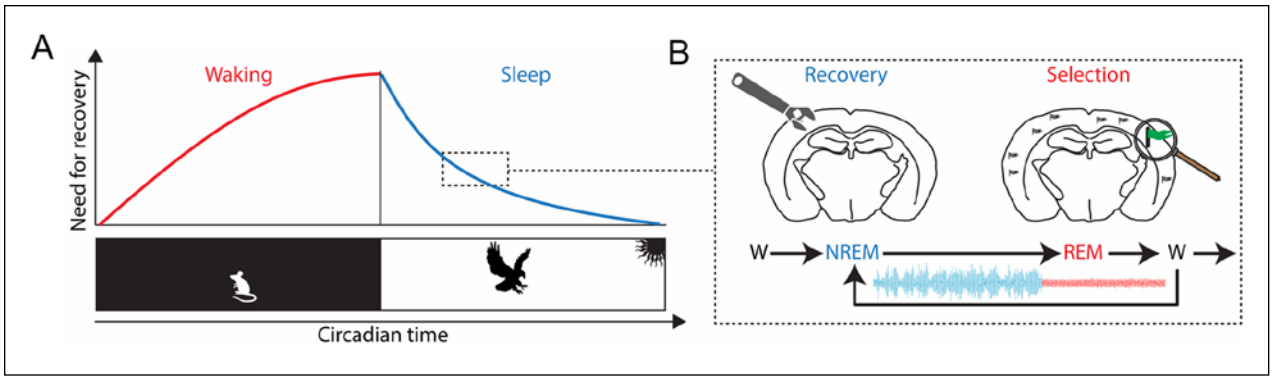

Figure 6. Overall summary of the hypothesis. (A) During waking the need for "recovery" increases progressively, necessitating the occurrence of sleep. During sleep, the need for recovery progressively declines until fully functional waking becomes possible. (B) In order to ensure that sleep functions are fulfilled as quickly and efficiently as possible, within sleep the brain switches regularly between two states, NREM sleep and REM sleep, which have distinct and complementary roles in the whole process. We posit that during NREM sleep slow oscillations various recovery processes, such as cellular maintenance or synaptic renormalisation, take place at the level of specific functionally interconnected networks. During an activated, wake-like brain state—REM sleep—neural networks that have obtained the necessary recovery during preceding NREM sleep are "selected" to be excluded from further recovery process. The remaining networks undergo recovery processes during the following NREM sleep episode. The animal wakes up spontaneously when the recovery is deemed complete for most essential networks, rendering the brain ready for optimal functioning during wakefulness.

1990). Whereas the circadian influence on the expression of REM sleep across the night likely plays a role, forced desynchrony studies showed that sleep-dependent increases in REM sleep could be partially uncoupled from the time of day (Dijk and Czeisler 1995). We propose that this observation can be accounted for by a low need for "selection" during REM sleep, when "recovery" provided by NREM sleep is still too far from being completed early on in the night. This may be related to the fact that the duration of REM sleep episode is determined by, or is proportional to, the number of brain circuits that have already obtained the necessary recovery during NREM sleep. If this is the case, it would be expected that REM sleep episodes get longer toward the end of a sleep period, when most circuits have already benefited from NREM sleep and the need to perform their offline performance testing before waking up becomes a high priority. The increasing trend in sleep spindles activity across the night, in parallel with decreasing sleep pressure (Dijk 1995; Knoblauch and others 2002; Olbrich and Achermann 2005; Vyazovskiy and others 2004b), is also consistent with our hypothesis that spindles reflect the process of tagging cortical networks for the selection process. On the other hand, several studies showed that chronic sleep restriction leads to a massive increase in REM sleep (Kim and others 2007; Leemburg and others 2010; Rechtschaffen and others 1999). We suggest that in this case, the occurrence of NREM-like activities during prolonged waking (Benington and Heller 1999; Vyazovskiy and others 2011) likely provides only a non-systematic, limited recovery to local networks only, while the selection process is prevented by actual waking behaviors. This necessitates longer and more frequent REM sleep episodes during subsequent sleep. Similar mechanisms can account for the occurrence of sleep-onset rapid eye movement periods (SOREMPs), which, while being more typical in pathological conditions, such as in narcolepsy (Baumann and others 2006; Rechtschaffen and others 1963), can also occur in healthy individuals. However, a significant association was noticed between the number of SOREMPs and how objectively sleepy the subjects were (Singh and others 2006), suggesting that in some cases the brain may be ready for the first round of "selection" before full-scale "recovery" begins.

Finally, our hypothesis is also in accord with the idea that in early ontogeny, REM (or active) sleep may serve to promote brain maturation and refinement of neurocircuitry (Mirmiran 1995; Mirmiran and Van Someren 1993; Roffwarg and others 1966). Specifically, it was suggested that spontaneous activity generated during "active sleep" in neonate rodents can contribute to the development of the somatosensory system (Tiriac and others 2012). The large quantities of REM sleep, typical for early ontogeny, could be expected if the proposed selection mechanism communicates that the brain is not yet ready for optimal functioning during the awake state. We suggest that at this stage, when the real waking experience is not yet available, the internal models of the body and the environment can only be generated based on a limited set of preexistent hard-wired programs, which are inherently simple and noisy because of the immaturity of developing brain networks (both cortical and subcortical). Because the representation of real waking simply does not exist, or is limited at this stage, REM episodes could

in theory last indefinitely, unless interrupted by external stimulation or spontaneously generated bursts of activity. With time, as experiences accumulate and neural circuits become better established and more refined, as facilitated initially by spontaneously generated patterns of motor activity (Blumberg 2010; Blumberg and others 2013), it becomes possible to perform the selection function in a more efficient manner. This would lead to a reduced duration of REM sleep with age.

Is REM Sleep Necessary for the Selection Process?

Both human and animal studies have shown that total sleep deprivation as well as selective deprivation of REM sleep are usually followed by a compensatory increase in REM sleep, although the effects reported are less consistent or smaller compared to the changes in NREM SWA (Benington and others 1994; Benington and others 1995; Endo and others 1997; Endo and others 1998; Franken 2002; Franken and others 1991; Vyazovskiy and others 2002; Werth and others 2002b). Moreover, some studies suggested that REM sleep can be largely eliminated pharmacologically without apparent consequences, at least with respect to learning and memory (Vertes and Eastman 2000). This raises a question as to whether REM sleep in general, and the proposed selection process in particular, is necessary at all. In our opinion, if it were redundant, it should be possible to eliminate REM sleep without affecting other brain states. However, the EEG in both waking and NREM sleep has been altered in phenelzine-treated patients (Landolt and Gillin 2002). Also, in rats, antidepressants that suppressed REM sleep also reduced EEG spindles at NREM-REM sleep transitions (Watts and others 2012), whereas selective REM sleep deprivation led to a reduction of SWA in NREM sleep (Benington and others 1994). Moreover, selective REM sleep deprivation in humans enhanced muscle atonia in NREM sleep (Werth and others 2002a). These studies suggest that REM sleep loss affects other states, although it is yet to be investigated whether the changes observed reflect physiological compensatory processes or a disruption in the normal regulation of brain states, which is maladaptive or pathological.

It cannot be excluded that the recovery and selection processes can occur concurrently, but only if different networks can undergo them independently, such as if they are located in different parts of the brain, or in light sleep stages only, toward the end of sleep period, when most brain networks have already recovered. Obviously, this imposes serious limitations on the extent to which the two processes can overlap in time and in space. It is likely that the emergence of two distinct sleep states—NREM sleep and REM sleep—separated from each other and from wakefulness, was necessary to ensure minimal interference between the functions of recovery and selection. The reasoning is that if the selection function were to occur in NREM sleep, it would likely be happening at the expense of its recovery function. On the other hand, intrusion of either recovery or selection processes into waking could in mild cases result in temporarily impaired behavioral performance (Vyazovskiy and others 2011), whereas in more severe cases could dramatically disrupt normal waking. It is tempting to suggest that some sleep disorders, such as narcolepsy (Saper and others 2010), or parasomnias, such as confusional arousals, REM sleep behavior disorder, sleep walking, or dream intrusions (Collerton and others 2005; Mahowald and others 2011; Terzaghi and others 2009; Terzaghi and others 2012), may ultimately arise from a breakdown of the proposed selection process. We would like to stress again that in such cases both NREM and REM sleep would be affected. Moreover, the manner in which this breakdown would be manifested can potentially take many different forms, from hallucinations, dreams enactment, and lack of muscle atonia during REM sleep in fatal familial insomnia (Montagna and Lugaresi 2002), to altered representation of oneself and the outside world in psychiatric disorders (Benca 1996; Peterson and Benca 2006; Wulff and others 2010).

Summary

In this Hypothesis article, we proposed a novel conceptual framework, according to which the phenomena occurring during sleep at many different spatial and temporal scales are causally interrelated (Fig. 6). We propose that after intense waking activity, all or most neurons in the neocortex need to express the slow oscillation to obtain "recovery" from preceding waking activity. During the up state of the slow oscillation, information transfer and synaptic plasticity, such as synaptic renormalization, take place within specific functionally interconnected neuronal networks. In turn, the down state allows for various cellular maintenance processes to occur. We hypothesize that within an individual NREM sleep episode, slow waves occur one after another until all functionally interconnected neuronal networks express a certain minimal number of uninterrupted slow oscillations, as dictated by their need for "recovery." This would terminate the episode of NREM sleep. Regular excursions into REM sleep play the role of a selection mechanism that determines which brain networks have already recovered and are ready for optimal functioning during waking. We hypothesize that the alternation of NREM and REM sleep episodes occurs throughout the entire sleep period, until all cortical networks have recovered from preceding waking (NREM sleep), and are selected to be excluded from

further recovery based on their offline performance (REM sleep). Thus, we propose that while the overall role of sleep is to ensure an optimal behavioral performance during subsequent waking, different kinds of sleep provide a distinct complementary contribution. Such an elaborate process is necessary given the complexity of the anatomical brain circuitry, the heterogeneity and functional specialization of the cortical networks, and to ensure that the process of recovery provided to specific brain networks is tailored to their preceding activity. This two-stage process, while providing an enormous evolutionary advantage and flexibility, likely appears prone to malfunction. We suggest that its breakdown may be a fundamental mechanism underlying many pathological conditions, from parasomnias to psychoses.

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References

Abel T, Havekes R, Saletin JM, Walker MP. 2013. Sleep, plasticity and memory from molecules to whole-brain networks. Curr Biol 23(17):R774–88.

Achermann P, Dijk DJ, Brunner DP, Borbely AA. 1993. A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. Brain Res Bull 31(1–2):97–113.

Albrecht D, Quaschling U, Zippel U, Davidowa H. 1996. Effects of dopamine on neurons of the lateral geniculate nucleus: an iontophoretic study. Synapse 23(2):70–8.

Altimus CM, Guler AD, Villa KL, McNeill DS, Legates TA, Hattar S. 2008. Rods-cones and melanopsin detect light and dark to modulate sleep independent of image formation. Proc Natl Acad Sci U S A 105(50):19998–20003.

Andrillon T, Nir Y, Staba RJ, Ferrarelli F, Cirelli C, Tononi G, and others. 2011. Sleep spindles in humans: insights from intracranial EEG and unit recordings. J Neurosci 31(49):17821–34.

Antal M, Acuna-Goycolea C, Pressler RT, Blitz DM, Regehr WG. 2010. Cholinergic activation of M2 receptors leads to context-dependent modulation of feedforward inhibition in the visual thalamus. PLoS Biol 8(4):e1000348.

Astori S, Wimmer RD, Prosser HM, Corti C, Corsi M, Liaudet N, and others. 2011. The Ca(V)3.3 calcium channel is the major sleep spindle pacemaker in thalamus. Proc Natl Acad Sci U S A 108(33):13823–8.

Baran B, Pace-Schott EF, Ericson C, Spencer RM. 2012. Processing of emotional reactivity and emotional memory over sleep. J Neurosci 32(3):1035–42.

Barbato G, Wehr TA. 1998. Homeostatic regulation of REM sleep in humans during extended sleep. Sleep 21(3):267–76.

Bartho P, Freund TF, Acsady L. 2002. Selective GABAergic innervation of thalamic nuclei from zona incerta. Eur J Neurosci 16(6):999–1014.

Battaglia FP, Sutherland GR, McNaughton BL. 2004. Hippocampal sharp wave bursts coincide with neocortical "up-state" transitions. Learn Mem 11(6):697–704.

Baumann CR, Khatami R, Werth E, Bassetti CL. 2006. Hypocretin (orexin) deficiency predicts severe objective excessive daytime sleepiness in narcolepsy with cataplexy. J Neurol Neurosurg Psychiatry 77(3):402–4.

Beersma DG, Dijk DJ, Blok CG, Everhardus I. 1990. REM sleep deprivation during 5 hours leads to an immediate REM sleep rebound and to suppression of non-REM sleep intensity. Electroencephalogr Clin Neurophysiol 76(2):114–22.

Benca RM. 1996. Sleep in psychiatric disorders. Neurol Clin 14(4):739–64.

Benington JH, Heller HC. 1994. Does the function of REM sleep concern non-REM sleep or waking? Prog Neurobiol 44(5):433–49.

Benington JH, Heller HC. 1999. Implications of sleep deprivation experiments for our understanding of sleep homeostasis. Sleep 22(8):1033–43.

Benington JH, Woudenberg MC, Heller HC. 1994. REM-sleep propensity accumulates during 2-h REM-sleep deprivation in the rest period in rats. Neurosci Lett 180(1):76–80.

Benington JH, Woudenberg MC, Heller HC. 1995. Apamin, a selective SK potassium channel blocker, suppresses REM sleep without a compensatory rebound. Brain Res 692(1–2):86–92.

Blitz DM, Regehr WG. 2005. Timing and specificity of feedforward inhibition within the LGN. Neuron 45(6):917–28.

Blumberg MS. 2010. Beyond dreams: do sleep-related movements contribute to brain development? Front Neurol 1:140.

Blumberg MS, Coleman CM, Gerth AI, McMurray B. 2013. Spatiotemporal structure of REM sleep twitching reveals developmental origins of motor synergies. Curr Biol 23(21):2011–9.

Boissard R, Gervasoni D, Schmidt MH, Barbagli B, Fort P, Luppi PH. 2002. The rat ponto-medullary network responsible for paradoxical sleep onset and maintenance: a combined microinjection and functional neuroanatomical study. Eur J Neurosci 16(10):1959–73.

Bokor H, Frere SG, Eyre MD, Slezia A, Ulbert I, Luthi A, and others. 2005. Selective GABAergic control of higher-order thalamic relays. Neuron 45(6):929–40.

Bonjean M, Baker T, Lemieux M, Timofeev I, Sejnowski T, Bazhenov M. 2011. Corticothalamic feedback controls sleep spindle duration in vivo. J Neurosci 31(25):9124–34.

Borbely AA. 1982. A two process model of sleep regulation. Hum Neurobiol 1(3):195–204.

Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW. 2012. Control of sleep and wakefulness. Physiol Rev 92(3):1087–187.

Buckelmuller J, Landolt HP, Stassen HH, Achermann P. 2006. Trait-like individual differences in the human sleep electroencephalogram. Neuroscience 138(1):351–6.

Burgess CR, Peever JH. 2013. A noradrenergic mechanism functions to couple motor behavior with arousal state. Curr Biol 23(18):1719–25.

Buzsáki G. 2006. Rhythms of the brain. Oxford, England: Oxford University Press.

Buzsaki G, Anastassiou CA, Koch C. 2012. The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes. Nat Rev Neurosci 13(6):407–20.

Buzsaki G, Logothetis N, Singer W. 2013. Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. Neuron 80(3):751–64.

Callaway CW, Lydic R, Baghdoyan HA, Hobson JA. 1987. Pontogeniculooccipital waves: spontaneous visual system activity during rapid eye movement sleep. Cell Mol Neurobiol 7(2):105–49.

Cantero JL, Atienza M, Stickgold R, Kahana MJ, Madsen JR, Kocsis B. 2003. Sleep-dependent theta oscillations in the human hippocampus and neocortex. J Neurosci 23(34):10897–903.

Carter ME, Adamantidis A, Ohtsu H, Deisseroth K, de Lecea L. 2009. Sleep homeostasis modulates hypocretin-mediated sleep-to-wake transitions. J Neurosci 29(35):10939–49.

Chow HM, Horovitz SG, Carr WS, Picchioni D, Coddington N, Fukunaga M, and others. 2013. Rhythmic alternating patterns of brain activity distinguish rapid eye movement sleep from other states of consciousness. Proc Natl Acad Sci U S A 110(25):10300–5.

Churchland PS. 2002. Brain-wise: studies in neurophilosophy. Cambridge, MA: MIT Press.

Cirelli C, Tononi G. 2008. Is sleep essential? PLoS Biol 6(8):e216.

Clement O, Sapin E, Libourel PA, Arthaud S, Brischoux F, Fort P, and others. 2012. The lateral hypothalamic area controls paradoxical (REM) sleep by means of descending projections to brainstem GABAergic neurons. J Neurosci 32(47):16763–74.

Collerton D, Perry E, McKeith I. 2005. Why people see things that are not there: a novel perception and attention deficit model for recurrent complex visual hallucinations. Behav Brain Sci 28(6):737–57.

Contreras D, Curro Dossi R, Steriade M. 1993. Electrophysiological properties of cat reticular thalamic neurones in vivo. J Physiol 470:273–94.

Contreras D, Destexhe A, Sejnowski TJ, Steriade M. 1996. Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback. Science 274(5288):771–4.

Crick F, Mitchison G. 1983. The function of dream sleep. Nature 304(5922):111–4.

Crunelli V, Hughes SW. 2009. The slow (<1 Hz) rhythm of non-REM sleep: a dialogue between three cardinal oscillators. Nat Neurosci 13(1):9–17.

Daan S, Beersma DG, Borbely AA. 1984. Timing of human sleep: recovery process gated by a circadian pacemaker. Am J Physiol 246(2 pt 2):R161–83.

Dang-Vu TT, Schabus M, Desseilles M, Sterpenich V, Bonjean M, Maquet P. 2010. Functional neuroimaging insights into the physiology of human sleep. Sleep 33(12):1589–603.

Datta S. 2010. Cellular and chemical neuroscience of mammalian sleep. Sleep Med 11(5):431–40.

Davies WL, Hankins MW, Foster RG. 2010. Vertebrate ancient opsin and melanopsin: divergent irradiance detectors. Photochem Photobiol Sci 9(11):1444–57.

Daya VG, Bentley AJ. 2010. Perception of experimental pain is reduced after provoked waking from rapid eye movement sleep. J Sleep Res 19(2):317–22.

De Gennaro L, Ferrara M. 2003. Sleep spindles: an overview. Sleep Med Rev 7(5):423–40.

Deboer T. 2013. Behavioral and electrophysiological correlates of sleep and sleep homeostasis. Curr Top Behav Neurosci Oct 19. [Epub ahead of print]

Delogu A, Sellers K, Zagoraiou L, Bocianowska-Zbrog A, Mandal S, Guimera J, and others. 2012. Subcortical visual shell nuclei targeted by ipRGCs develop from a Sox14+-GABAergic progenitor and require Sox14 to regulate daily activity rhythms. Neuron 75(4):648–62.

Dement W. 1958. The occurrence of low voltage, fast, electroencephalogram patterns during behavioral sleep in the cat. Electroencephalogr Clin Neurophysiol 10(2):291–6.

Destexhe A, Contreras D, Steriade M. 1999. Spatiotemporal analysis of local field potentials and unit discharges in cat cerebral cortex during natural wake and sleep states. J Neurosci 19(11):4595–608.

Destexhe A, Hughes SW, Rudolph M, Crunelli V. 2007. Are corticothalamic "up" states fragments of wakefulness? Trends Neurosci 30(7):334–42.

Diekelmann S, Born J. 2010. The memory function of sleep. Nat Rev Neurosci 11(2):114–26.

Dijk DJ. 1995. EEG slow waves and sleep spindles: windows on the sleeping brain. Behav Brain Res 69(1–2):109–16.

Dijk DJ, Czeisler CA. 1995. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci 15(5 pt 1):3526–38.

El Helou J, Belanger-Nelson E, Freyburger M, Dorsaz S, Curie T, La Spada F, and others. 2013. Neuroligin-1 links neuronal activity to sleep-wake regulation. Proc Natl Acad Sci U S A 110(24):9974–9.

Endo T, Roth C, Landolt HP, Werth E, Aeschbach D, Achermann P, and others. 1998. Selective REM sleep deprivation in humans: effects on sleep and sleep EEG. Am J Physiol 274(4 pt 2):R1186–94.

Endo T, Schwierin B, Borbely AA, Tobler I. 1997. Selective and total sleep deprivation: effect on the sleep EEG in the rat. Psychiatry Res 66(2–3):97–110.

Fisher SP, Foster RG, Peirson SN. 2013. The circadian control of sleep. Handb Exp Pharmacol (217):157–83.

Fort P, Bassetti CL, Luppi PH. 2009. Alternating vigilance states: new insights regarding neuronal networks and mechanisms. Eur J Neurosci 29(9):1741–53.

Franken P. 2002. Long-term vs. short-term processes regulating REM sleep. J Sleep Res 11(1):17–28.

Franken P, Chollet D, Tafti M. 2001. The homeostatic regulation of sleep need is under genetic control. J Neurosci 21(8):2610–21.

Franken P, Dijk DJ, Tobler I, Borbely AA. 1991. Sleep deprivation in rats: effects on EEG power spectra, vigilance states, and cortical temperature. Am J Physiol 261(1 pt 2):R198–208.

Franken P, Malafosse A, Tafti M. 1998. Genetic variation in EEG activity during sleep in inbred mice. Am J Physiol 275(4 pt 2):R1127–37.

Gervasoni D, Darracq L, Fort P, Souliere F, Chouvet G, Luppi PH. 1998. Electrophysiological evidence that noradrenergic neurons of the rat locus coeruleus are tonically inhibited by GABA during sleep. Eur J Neurosci 10(3):964–70.

Grosmark AD, Mizuseki K, Pastalkova E, Diba K, Buzsaki G. 2012. REM sleep reorganizes hippocampal excitability. Neuron 75(6):1001–7.

Grush R. 2004. The emulation theory of representation: motor control, imagery, and perception. Behav Brain Sci 27(3):377–96.

Gujar N, McDonald SA, Nishida M, Walker MP. 2011. A role for REM sleep in recalibrating the sensitivity of the human brain to specific emotions. Cereb Cortex 21(1):115–23.

Hankins MW, Peirson SN, Foster RG. 2008. Melanopsin: an exciting photopigment. Trends Neurosci 31(1):27–36.

Hassani OK, Henny P, Lee MG, Jones BE. 2010. GABAergic neurons intermingled with orexin and MCH neurons in the lateral hypothalamus discharge maximally during sleep. Eur J Neurosci 32(3):448–57.

Hassani OK, Lee MG, Jones BE. 2009. Melanin-concentrating hormone neurons discharge in a reciprocal manner to orexin neurons across the sleep-wake cycle. Proc Natl Acad Sci U S A 106(7):2418–22.

Hatori M, Le H, Vollmers C, Keding SR, Tanaka N, Buch T, and others. 2008. Inducible ablation of melanopsin-expressing retinal ganglion cells reveals their central role in non-image forming visual responses. PLoS One 3(6):e2451.

Hattar S, Kumar M, Park A, Tong P, Tung J, Yau KW, and others. 2006. Central projections of melanopsin-expressing retinal ganglion cells in the mouse. J Comp Neurol 497(3):326–49.

Hattar S, Liao HW, Takao M, Berson DM, Yau KW. 2002. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. Science 295(5557):1065–70.

Henley K, Morrison AR. 1974. A re-evaluation of the effects of lesions of the pontine tegmentum and locus coeruleus on phenomena of paradoxical sleep in the cat. Acta Neurobiol Exp (Wars) 34(2):215–32.

Hobson JA. 2009. REM sleep and dreaming: towards a theory of protoconsciousness. Nat Rev Neurosci 10(11):803–13.

Hobson JA, McCarley RW, Wyzinski PW. 1975. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 189(4196):55–8.

Horne J. 2013. Why REM sleep? Clues beyond the laboratory in a more challenging world. Biol Psychol 92(2):152–68.

Horne JA. 2000. REM sleep—by default? Neurosci Biobehav Rev 24(8):777–97.

Huber R, Deboer T, Tobler I. 2000. Effects of sleep deprivation on sleep and sleep EEG in three mouse strains: empirical data and simulations. Brain Res 857(1–2):8–19.

Jego S, Glasgow SD, Herrera CG, Ekstrand M, Reed SJ, Boyce R, and others. 2013. Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus. Nat Neurosci 16(11):1637–43.

Jones BE. 2004. Paradoxical REM sleep promoting and permitting neuronal networks. Arch Ital Biol 142(4):379–96.

Jouvet M. 1965. Paradoxical sleep—a study of its nature and mechanisms. Prog Brain Res 18:20–62.

Kantor S, Mochizuki T, Janisiewicz AM, Clark E, Nishino S, Scammell TE. 2009. Orexin neurons are necessary for the circadian control of REM sleep. Sleep 32(9):1127–34.

Karashima A, Katayama N, Nakao M. 2010. Enhancement of synchronization between hippocampal and amygdala theta waves associated with pontine wave density. J Neurophysiol 103(5):2318–25.

Karni A, Tanne D, Rubenstein BS, Askenasy JJ, Sagi D. 1994. Dependence on REM sleep of overnight improvement of a perceptual skill. Science 265(5172):679–82.

Kilduff TS, Cauli B, Gerashchenko D. 2011. Activation of cortical interneurons during sleep: an anatomical link to homeostatic sleep regulation? Trends Neurosci 34(1):10–9.

Kim Y, Laposky AD, Bergmann BM, Turek FW. 2007. Repeated sleep restriction in rats leads to homeostatic and allostatic responses during recovery sleep. Proc Natl Acad Sci U S A 104(25):10697–702.

Kleitman N. 1982. Basic rest-activity cycle—22 years later. Sleep 5(4):311–7.

Knoblauch V, Krauchi K, Renz C, Wirz-Justice A, Cajochen C. 2002. Homeostatic control of slow-wave and spindle frequency activity during human sleep: effect of differential sleep pressure and brain topography. Cereb Cortex 12(10):1092–100.

Krueger JM, Obal F. 1993. A neuronal group theory of sleep function. J Sleep Res 2(2):63–69.

Krueger JM, Rector DM, Roy S, Van Dongen HP, Belenky G, Panksepp J. 2008. Sleep as a fundamental property of neuronal assemblies. Nat Rev Neurosci 9(12):910–9.

Krueger JM, Tononi G. 2011. Local use-dependent sleep; synthesis of the new paradigm. Curr Top Med Chem 11(19):2490–2.

Landolt HP, Gillin JC. 2002. Different effects of phenelzine treatment on EEG topography in waking and sleep in depressed patients. Neuropsychopharmacology 27(3): 462–9.

Leemburg S, Vyazovskiy VV, Olcese U, Bassetti CL, Tononi G, Cirelli C. 2010. Sleep homeostasis in the rat is preserved during chronic sleep restriction. Proc Natl Acad Sci U S A 107(36):15939–44.

LeGates TA, Altimus CM, Wang H, Lee HK, Yang S, Zhao H, and others. 2012. Aberrant light directly impairs mood and learning through melanopsin-expressing neurons. Nature 491(7425):594–8.

Lu J, Bjorkum AA, Xu M, Gaus SE, Shiromani PJ, Saper CB. 2002. Selective activation of the extended ventrolateral preoptic nucleus during rapid eye movement sleep. J Neurosci 22(11):4568–76.

Lu J, Sherman D, Devor M, Saper CB. 2006. A putative flip-flop switch for control of REM sleep. Nature 441(7093):589–94.

Luczak A, Bartho P, Marguet SL, Buzsaki G, Harris KD. 2007. Sequential structure of neocortical spontaneous activity in vivo. Proc Natl Acad Sci U S A 104(1):347–52.

Lupi D, Oster H, Thompson S, Foster RG. 2008. The acute light-induction of sleep is mediated by OPN4-based photoreception. Nat Neurosci 11(9):1068–73.

Luthi A. 2013. Sleep spindles: where they come from, what they do. Neuroscientist Aug 27. [Epub ahead of print]

Mackiewicz M, Shockley KR, Romer MA, Galante RJ, Zimmerman JE, Naidoo N, and others. 2007. Macromolecule biosynthesis: a key function of sleep. Physiol Genomics 31(3):441–57.

Mahowald MW, Cramer Bornemann MA, Schenck CH. 2011. State dissociation, human behavior, and consciousness. Curr Top Med Chem 11(19):2392–402.

Maquet P, Ruby P, Maudoux A, Albouy G, Sterpenich V, Dang-Vu T, and others. 2005. Human cognition during REM sleep and the activity profile within frontal and parietal cortices: a reappraisal of functional neuroimaging data. Prog Brain Res 150:219–27.

Maret S, Dorsaz S, Gurcel L, Pradervand S, Petit B, Pfister C, and others. 2007. Homer1a is a core brain molecular correlate of sleep loss. Proc Natl Acad Sci U S A 104(50):20090–5.

Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G. 2004. The sleep slow oscillation as a traveling wave. J Neurosci 24(31):6862–70.

McCarley RW, Hobson JA. 1975. Neuronal excitability modulation over the sleep cycle: a structural and mathematical model. Science 189(4196):58–60.

Mignot E, Taheri S, Nishino S. 2002. Sleeping with the hypothalamus: emerging therapeutic targets for sleep disorders. Nat Neurosci 5(suppl):1071–5.

Millstein J, Winrow CJ, Kasarskis A, Owens JR, Zhou L, Summa KC, and others. 2011. Identification of causal genes, networks, and transcriptional regulators of REM sleep and wake. Sleep 34(11):1469–77.

Mirmiran M. 1995. The function of fetal/neonatal rapid eye movement sleep. Behav Brain Res 69(1–2):13–22.

Mirmiran M, Van Someren E. 1993. Symposium: normal and abnormal REM sleep regulation: the importance of REM sleep for brain maturation. J Sleep Res 2(4):188–92.

Montagna P, Lugaresi E. 2002. Agrypnia excitata: a generalized overactivity syndrome and a useful concept in the neurophysiopathology of sleep. Clin Neurophysiol 113(4):552–60.

Morairty SR, Dittrich L, Pasumarthi RK, Valladao D, Heiss JE, Gerashchenko D, and others. 2013. A role for cortical nNOS/NK1 neurons in coupling homeostatic sleep drive to EEG slow wave activity. Proc Natl Acad Sci U S A 110(50):20272–7.

Morin LP. 2013. Neuroanatomy of the extended circadian rhythm system. Exp Neurol 243:4–20.

Morin LP, Blanchard JH. 1999. Forebrain connections of the hamster intergeniculate leaflet: comparison with those of ventral lateral geniculate nucleus and retina. Vis Neurosci 16(6):1037–54.

Morin LP, Blanchard JH. 2005. Descending projections of the hamster intergeniculate leaflet: relationship to the sleep/arousal and visuomotor systems. J Comp Neurol 487(2):204–16.

Mouret J, Delorme F, Jouvet M. 1967. Lesions of the pontine tegmentum and sleep in rats. C R Seances Soc Biol Fil 161(7):1603–6.

Munsch T, Yanagawa Y, Obata K, Pape HC. 2005. Dopaminergic control of local interneuron activity in the thalamus. Eur J Neurosci 21(1):290–4.

Nir Y, Staba RJ, Andrillon T, Vyazovskiy VV, Cirelli C, Fried I, and others. 2011. Regional slow waves and spindles in human sleep. Neuron 70(1):153–69.

Nishida M, Pearsall J, Buckner RL, Walker MP. 2009. REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cereb Cortex 19(5):1158–66.

Ocampo-Garces A, Vivaldi EA. 2002. Short-term homeostasis of REM sleep assessed in an intermittent REM sleep deprivation protocol in the rat. J Sleep Res 11(1):81–9.

Olbrich E, Achermann P. 2005. Analysis of oscillatory patterns in the human sleep EEG using a novel detection algorithm. J Sleep Res 14(4):337–46.

Parmeggiani PL. 2003. Thermoregulation and sleep. Front Biosci 8:S557–67.

Peirson S, Foster RG. 2006. Melanopsin: another way of signaling light. Neuron 49(3):331–9.

Perogamvros L, Dang-Vu TT, Desseilles M, Schwartz S. 2013. Sleep and dreaming are for important matters. Front Psychol 4:474.

Peterson MJ, Benca RM. 2006. Sleep in mood disorders. Psychiatr Clin North Am 29(4):1009–32.

Poe GR, Walsh CM, Bjorness TE. 2010. Cognitive neuroscience of sleep. Prog Brain Res 185:1–19.

Rasch B, Born J. 2013. About sleep's role in memory. Physiol Rev 93(2):681–766.

Rechtschaffen A, Bergmann BM, Gilliland MA, Bauer K. 1999. Effects of method, duration, and sleep stage on rebounds from sleep deprivation in the rat. Sleep 22(1):11–31.

Rechtschaffen A, Wolpert EA, Dement WC, Mitchell SA, Fisher C. 1963. Nocturnal sleep of narcoleptics. Electroencephalogr Clin Neurophysiol 15:599–609.

Ribeiro S, Nicolelis MA. 2004. Reverberation, storage, and postsynaptic propagation of memories during sleep. Learn Mem 11(6):686–96.

Riedner BA, Hulse BK, Murphy MJ, Ferrarelli F, Tononi G. 2011. Temporal dynamics of cortical sources underlying spontaneous and peripherally evoked slow waves. Prog Brain Res 193:201–18.

Riedner BA, Vyazovskiy VV, Huber R, Massimini M, Esser S, Murphy M, and others. 2007. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. Sleep 30(12):1643–57.

Roffwarg HP, Muzio JN, Dement WC. 1966. Ontogenetic development of the human sleep-dream cycle. Science 152(3722):604–19.

Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. 2010. Sleep state switching. Neuron 68(6):1023–42.

Saper CB, Scammell TE, Lu J. 2005. Hypothalamic regulation of sleep and circadian rhythms. Nature 437(7063):1257–63.

Sapin E, Lapray D, Berod A, Goutagny R, Leger L, Ravassard P, and others. 2009. Localization of the brainstem GABAergic neurons controlling paradoxical (REM) sleep. PLoS One 4(1):e4272.

Sastre JP, Buda C, Kitahama K, Jouvet M. 1996. Importance of the ventrolateral region of the periaqueductal gray and adjacent tegmentum in the control of paradoxical sleep as studied by muscimol microinjections in the cat. Neuroscience 74(2):415–26.

Scharf MT, Naidoo N, Zimmerman JE, Pack AI. 2008. The energy hypothesis of sleep revisited. Prog Neurobiol 86(3):264–80.

Sejnowski TJ, Destexhe A. 2000. Why do we sleep? Brain Res 886(1–2):208–223.

Siegel JM. 2005. Clues to the functions of mammalian sleep. Nature 437(7063):1264–71.

Siegel JM. 2011. REM sleep: a biological and psychological paradox. Sleep Med Rev 15(3):139–42.

Singh M, Drake CL, Roth T. 2006. The prevalence of multiple sleep-onset REM periods in a population-based sample. Sleep 29(7):890–5.

Sirota A, Buzsaki G. 2005. Interaction between neocortical and hippocampal networks via slow oscillations. Thalamus Relat Syst 3(4):245–59.

Smith C. 1985. Sleep states and learning: a review of the animal literature. Neurosci Biobehav Rev 9(2):157–68.

Steriade M. 2006. Grouping of brain rhythms in corticothalamic systems. Neuroscience 137(4):1087–106.

Steriade M, Timofeev I, Grenier F. 2001. Natural waking and sleep states: a view from inside neocortical neurons. J Neurophysiol 85(5):1969–85.

Stickgold R. 1998. Sleep: off-line memory reprocessing. Trends Cogn Sci 2(12):484–92.

Studholme KM, Gompf HS, Morin LP. 2013. Brief light stimulation during the mouse nocturnal activity phase simultaneously induces a decline in core temperature and locomotor activity followed by EEG-determined sleep. Am J Physiol Regul Integr Comp Physiol 304(6):R459–71.

Szymusiak R, McGinty D. 2008. Hypothalamic regulation of sleep and arousal. Ann N Y Acad Sci 1129:275–86.

Tassi P, Bonnefond A, Engasser O, Hoeft A, Eschenlauer R, Muzet A. 2006. EEG spectral power and cognitive performance during sleep inertia: the effect of normal sleep duration and partial sleep deprivation. Physiol Behav 87(1):177–84.

Terenzi MG, Zagon A, Roberts MH. 1995. Efferent connections from the anterior pretectal nucleus to the diencephalon and mesencephalon in the rat. Brain Res 701(1–2):183–91.

Terzaghi M, Sartori I, Tassi L, Didato G, Rustioni V, LoRusso G, and others. 2009. Evidence of dissociated arousal states during NREM parasomnia from an intracerebral neurophysiological study. Sleep 32(3):409–12.

Terzaghi M, Sartori I, Tassi L, Rustioni V, Proserpio P, Lorusso G, and others. 2012. Dissociated local arousal states underlying essential clinical features of non-rapid eye movement arousal parasomnia: an intracerebral stereoelectroencephalographic study. J Sleep Res 21(5):502–6.

Timofeev I. 2013. Local origin of slow EEG waves during sleep. Zh Vyssh Nerv Deiat Im I P Pavlova 63(1):105–12.

Tiriac A, Uitermarkt BD, Fanning AS, Sokoloff G, Blumberg MS. 2012. Rapid whisker movements in sleeping newborn rats. Curr Biol 22(21):2075–80.

Tobler I. 2005. Phylogeny of sleep regulation. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia, PA: W. B. Saunders.

Tononi G, Cirelli C. 2006. Sleep function and synaptic homeostasis. Sleep Med Rev 10(1):49–62.

Trachsel L, Tobler I, Achermann P, Borbely AA. 1991. Sleep continuity and the REM-nonREM cycle in the rat under baseline conditions and after sleep deprivation. Physiol Behav 49(3):575-80.

Tsai JW, Hannibal J, Hagiwara G, Colas D, Ruppert E, Ruby NF, and others. 2009. Melanopsin as a sleep modulator: circadian gating of the direct effects of light on sleep and altered sleep homeostasis in Opn4(-/-) mice. PLoS Biol 7(6):e1000125.

Vanini G, Torterolo P, McGregor R, Chase MH, Morales FR. 2007. GABAergic processes in the mesencephalic tegmentum modulate the occurrence of active (rapid eye movement) sleep in guinea pigs. Neuroscience 145(3):1157–67.

Vertes RP, Eastman KE. 2000. The case against memory consolidation in REM sleep. Behav Brain Sci 23(6):867–76.

Vidal L, Blanchard J, Morin LP. 2005. Hypothalamic and zona incerta neurons expressing hypocretin, but not melanin concentrating hormone, project to the hamster intergeniculate leaflet. Neuroscience 134(3):1081–90.

Vrang N, Mrosovsky N, Mikkelsen JD. 2003. Afferent projections to the hamster intergeniculate leaflet demonstrated by retrograde and anterograde tracing. Brain Res Bull 59(4):267–88.

Vyazovskiy V, Achermann P, Borbely AA, Tobler I. 2004a. Interhemispheric coherence of the sleep electroencephalogram in mice with congenital callosal dysgenesis. Neuroscience 124(2):481–8.

Vyazovskiy VV, Achermann P, Borbely AA, Tobler I. 2004b. The dynamics of spindles and EEG slow-wave activity in NREM sleep in mice. Arch Ital Biol 142(4):511–23.

Vyazovskiy VV, Borbely AA, Tobler I. 2002. Interhemispheric sleep EEG asymmetry in the rat is enhanced by sleep deprivation. J Neurophysiol 88(5):2280–6.

Vyazovskiy VV, Harris KD. 2013. Sleep and the single neuron: the role of global slow oscillations in individual cell rest. Nat Rev Neurosci 14(6):443–51.

Vyazovskiy VV, Olcese U, Hanlon EC, Nir Y, Cirelli C, Tononi G. 2011. Local sleep in awake rats. Nature 472(7344):443–7.

Vyazovskiy VV, Olcese U, Lazimy YM, Faraguna U, Esser SK, Williams JC, and others. 2009. Cortical firing and sleep homeostasis. Neuron 63(6):865–78.

Vyazovskiy VV, Riedner BA, Cirelli C, Tononi G. 2007a. Sleep homeostasis and cortical synchronization: II. A local field potential study of sleep slow waves in the rat. Sleep 30(12):1631–42.

Vyazovskiy VV, Ruijgrok G, Deboer T, Tobler I. 2006. Running wheel accessibility affects the regional electroencephalogram during sleep in mice. Cereb Cortex 16(3):328–36.

Vyazovskiy VV, Tobler I. 2005. Regional differences in NREM sleep slow-wave activity in mice with congenital callosal dysgenesis. J Sleep Res 14(3):299–304.

Vyazovskiy VV, Tobler I. 2012. The temporal structure of behaviour and sleep homeostasis. PLoS One 7(12):e50677.

Vyazovskiy VV, Tobler I, Winsky-Sommerer R. 2007b. Alteration of behavior in mice by muscimol is associated with regional electroencephalogram synchronization. Neuroscience 147(3):833–41.

Watts A, Gritton HJ, Sweigart J, Poe GR. 2012. Antidepressant suppression of non-REM sleep spindles and REM sleep impairs hippocampus-dependent learning while augmenting striatum-dependent learning. J Neurosci 32(39):13411–20.

Werth E, Achermann P, Borbely AA. 2002a. Selective REM sleep deprivation during daytime. II. Muscle atonia in non-REM sleep. Am J Physiol Regul Integr Comp Physiol 283(2):R527–32.

Werth E, Cote KA, Gallmann E, Borbely AA, Achermann P. 2002b. Selective REM sleep deprivation during daytime I. Time course of interventions and recovery sleep. Am J Physiol Regul Integr Comp Physiol 283(2):R521–6.

Wisor JP. 2012. A metabolic-transcriptional network links sleep and cellular energetics in the brain. Pflugers Arch 463(1):15–22.

Wulff K, Gatti S, Wettstein JG, Foster RG. 2010. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat Rev Neurosci 11(8):589–99.

Xi MC, Morales FR, Chase MH. 1999. Evidence that wakefulness and REM sleep are controlled by a GABAergic pontine mechanism. J Neurophysiol 82(4):2015–9.

Zamboni G, Perez E, Amici R, Jones CA, Parmeggiani PL. 1999. Control of REM sleep: an aspect of the regulation of physiological homeostasis. Arch Ital Biol 137(4):249-62.

Zhao Y, Kerscher N, Eysel U, Funke K. 2002. D1 and D2 receptor-mediated dopaminergic modulation of visual responses in cat dorsal lateral geniculate nucleus. J Physiol 539(pt 1):223–38.